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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,263	03/21/2002	Hermona Soreq	2391-00101	1307
7590	08/05/2004		EXAMINER WEGERT, SANDRA L	
Kenneth I Kohn Kohn & Associates 30500 Northwestern Highway suite 410 Farmington Hills, MI 48334			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 08/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/980,263

Applicant(s)

SOREQ ET AL.

Examiner

Sandra Wegert

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 May 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 5-16 is/are pending in the application.
- 4a) Of the above claim(s) 6-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2 and 5 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 November 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 2 May 2002
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed 4 May 2004 has been entered. The Information Disclosure Citation, submitted 2 May 2002, has been entered. Claims 3 and 4 are canceled. Claims 1 and 5 are amended. Claims 6-15 were withdrawn by the examiner (20 December 2003). Claims 1, 2 and 5 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a previous Office action.

Withdrawn Objections and/or Rejections

Abstract

The objection to the Specification for lacking an Abstract, as set forth at page 3 of the previous Office Action (20 December 2003), is *withdrawn* in view of the Abstract submitted by the Applicant (4 May 2004).

Claim Objections

The objections to Claims 1 and 4 for reciting non-elected inventions (i.e., "blood-brain-barrier," "Alzheimer's disease," and SEQ ID NO: 2 and 3) are *withdrawn*. Applicant amended Claim 1 to remove references to non-elected inventions and cancelled Claim 4 (4 May 2004).

Claim Rejections- 35 USC § 102

The rejection of Claim 1 under 35 U.S.C. 102(b) as being unpatentable over Boschetti, et

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al, (1996, Clinical Chem., 42(1): 19-23), is *withdrawn*. Applicants amended Claim 1 (4 May 2004) to recite SEQ ID NO: 1, which has low homology to the acetylcholinesterase C-terminal of the Boschetti, et al reference.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, first paragraph – scope of enablement.

Claims 1, 2 and 5 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for an antibody that binds the acetylcholinesterase fragment peptide of SEQ ID NO: 1, to be used for identifying production of the AChE splice variant in the brains of mice, does not enable an antibody for diagnosing central nervous system stress in animals or humans, or for identifying production of the AChE splice variant in animals other than mice. The reasons for this rejection under 35 USC 112, first paragraph, are set forth at pp. 3-7 of the previous Office Action (4 May 2004). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims.

The claims are directed to an antibody that recognizes the I4 polypeptide of SEQ ID NO: 1, for diagnosing central nervous system stress. Dependent claims read on stress caused by psychological, chemical or physical insult and an antibody that is monoclonal.

Applicants have not demonstrated that they have diagnosed a "central nervous system stress," but instead demonstrated expression of the AChE-R variant in the hippocampi of mice forced to swim in the "confined swim stress" test. AChE-R splice variant expression is shown

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by Western blot in glioblastoma samples (Figure 1), labeled as "stressed" or "non-stressed," as well as mice transfected with the glioblastoma AChE-R splice variant (Figure 2). Similar measurements were made in the cerebral spinal fluid of Alzheimer's disease patients, using an antibody against *alpha-ARP*, a protein with an unknown relationship or correlation to the AChE-R splice variant identified by SEQ ID NO: 1.

Although the experiments with human cerebral spinal fluid refer to "stressed" versus "non-stressed" humans, it should be kept in mind that stress is defined in a circular way in the instant Specification:

"Non-stressed humans" refers to patients in which no enhanced Omnipaque signal was detected by CT brain scan, while "stressed humans" refers to patients in which an enhanced Omnipaque signal was detected by CT brain scan" (Specification, page 20).

This means that "stressed" humans are those that gave a positive result in the Applicant's test. Furthermore, the specification does not enable use of the mouse antibody against the splice variant of AChE to diagnose a "central nervous system (CNS) stress" in humans, or in other animals besides mice. Unless and until it is confirmed that AChE splice variants are the same in mice and humans, the claimed antibody cannot be used to diagnose any conditions in humans. And, since "central nervous system (CNS) stress" is poorly defined in the instant Specification, and may encompass a variety of neurological disorders (such as stroke, drug overdose and cancer, for example), and since the instant Specification is enabling only for identifying production of AChE-R in mice, a more specific phrase is needed to describe the condition the Applicant is intending to diagnose. The Specification describes use of antibodies made to SEQ ID NO: 1 to identify production of the AChE-R splice variant in mice hippocampi after the mice were subjected to a swim stress test. Aside from identification of the AChE-R splice variant in

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mice, diagnosis of a "central nervous system (CNS) stress", as claimed, is not adequately disclosed.

Applicants discuss the relationship of AChE and "central nervous system stress" in the Response of 4 May 2004 (page 6):

"Further support for the definition of "central nervous system stress" can be found in other publications where there is disclosed that the switch from AChE-S to AChE-R, is indeed a reliable indication of CNS stress regardless of what triggered the condition. This has been demonstrated in mice following physical stress such as head injury (Shoham et al. 2000), chemical stress (exposure to organophosphates) (Kaufer, et al. 1999), immobilization stress (Nijholt et al. 2004), switch of day-to-night stress (Cohen et al. 2002), and in humans under neurological disease (Tomkims et al. 2002) and following LPS exposure (Cohen et al. 2003). Accordingly, there is sufficient support in the specification as filed for the use of central nervous system stress as recited in the claims. Reconsideration of the rejection is respectfully requested."

Applicant's arguments filed 4 May 2004 have been fully considered but are not deemed persuasive for the following reasons:

The examiner could not locate "Shoham, et al (2000)". A paper by Sternfeld, Shoham, et al (2000, PNAS, 97(15): 8647-8652) discusses a variant acetylcholinesterase in mice, but only hints at its relationship to head injury in the discussion (page 8651). "Kaufer, et al. 1999" might refer to the Kaufer, D. and Soreq, H. paper (1999, Curr. Opin. Neurol., 12(6): 739-743) in which cholinesterase inhibition is discussed in light of several neurological diseases, but makes no mention of the AChE variant in either mice or humans. "Nijholt et al. 2004" might refer to a recent paper, similar to the instant Specification, in which a variant acetylcholinesterase is detected in mice after "contextual fear" experiments (Nijholt, et al, 2004, Mol. Psychiatry, 9: 174-

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183). However, in Nijholt, et al, 2004, a possible human cholinesterase variant is not revealed or discussed. What references were indicated by "Cohen et al. 2002," "Tomkims et al. 2002," and "Cohen et al. 2003" could not be inferred by the examiner. Applicants are encouraged to submit any possible evidence in the form of a Declaration, under 37 CFR 1.132, preferably with complete copies of the literature references.

In summary, the specification does not provide a description of a repeatable process of producing, nor of working examples of making, antibodies to the mouse acetylcholinesterase splice variant for the purpose of diagnosing "central nervous system stress" in subjects that may include humans and may include "stresses" that are dissimilar to physical stress in normal mice. Nor can antibodies to AChE-R be used to identify changes in the brain of humans or animals, other than in mice subjected to standard tests that provoke anxiety or fear.

Proper analysis of the Wands factors were provided in the previous Office Action. Due to the large quantity of experimentation required to determine how to: use antibodies against splice variants of acetylcholinesterase (SEQ ID NO: 1) to diagnose a "central nervous system (CNS) stress," the lack of direction or guidance in the specification regarding the conditions that can be diagnosed using such antibodies, the lack of working examples whereby "central nervous system (CNS) stress[es]" are identified or diagnosed, and the breadth of the claims which embrace diagnosis of conditions in humans using the mouse antibody -undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

References used for a general understanding of the art:

Li, et al, 1991, J. Biol. Chem, 266(34): 23083-23090.

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Loft, A., 1995, Danish Medical Bulletin, 42(1): 54-70.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

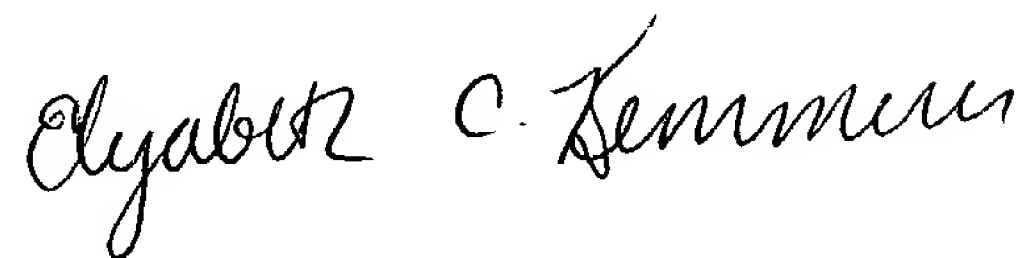
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The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW

30 July 2004

A handwritten signature in cursive script that reads "Elizabeth C. Kemmerer".

ELIZABETH KEMMERER
PRIMARY EXAMINER